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Intellectual property rights and challenges for development of affordable human papillomavirus, rotavirus and pneumococcal vaccines: Patent landscaping and perspectives of developing country vaccine manufacturers

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ABSTRACT

The success of Gavi, the Vaccine Alliance depends on the vaccine markets providing appropriate, affordable vaccines at sufficient and reliable quantities. Gavi's current supplier base for new and underutilized vaccines, such as the human papillomavirus (HPV), rotavirus, and the pneumococcal conjugate vaccine is very small. There is growing concern that following globalization of laws on intellectual property rights (IPRs) through trade agreements, IPRs are impeding new manufacturers from entering the market with competing vaccines. This article examines the extent to which IPRs, specifically patents, can create such obstacles, in particular for developing country vaccine manufacturers (DCVMs). Through building patent landscapes in Brazil, China, and India and interviews with manufacturers and experts in the field, we found intense patenting activity for the HPV and pneumococcal vaccines that could potentially delay the entry of new manufacturers. Increased transparency around patenting of vaccine technologies, stricter patentability criteria suited for local development needs and strengthening of IPRs management capabilities where relevant, may help reduce impediments to market entry for new manufacturers and ensure a competitive supplier base for quality vaccines at sustainably low prices.

1. Introduction

Established in 2000, Gavi is a public private partnership that facilitates access to lifesaving vaccines for low-income countries, using an innovative model to pool donor funds and support country immunization priorities. From inception to December 2013, Gavi had invested US$8.7 billion in over 70 countries, helping to prevent over six million future deaths through immunization. Gavi's success depends on the vaccine markets providing appropriate, affordable vaccines at sufficient and reliable quantities. "Shaping vaccine markets" is therefore, one of four strategic goals in the Gavi Alliance strategy 2011–2015 [1]. The aim is to ensure an adequate supply of quality vaccines that meet demand at low and sustainable prices. Through targeted interventions and strategic procurement, Gavi tries to encourage new vaccine manufacturers to enter the market as a means to increase competition, thereby increasing supply and putting a downward pressure on prices [2].

The current supplier base for many of the new vaccines purchased by Gavi is very small, but progress has been made in some product markets: in 2001, Gavi began to procure pentavalent vaccines—which combine the antigens for five infectious diseases in a single shot—from just one manufacturer [3]. By 2014, this has increased to six manufacturers, two of which are based in India. While historically, manufacturers based in the United States and Europe have dominated most vaccine markets, development and manufacturing capacity has increased in other parts of the world over the last two decades [2]. Nevertheless, no developing country manufacturers have yet brought follow-on versions of newer

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vaccines, such as the human papillomavirus (HPV), rotavirus, and pneumococcal conjugate vaccines to market [3–5].

Simultaneously, international trade agreements require countries with vaccine manufacturing capabilities to provide patent protection for pharmaceutical and biological products under the WTO agreement on trade-related aspects of intellectual property (TRIPS). This article summarizes the results of a study funded by Gavi, which explored whether patents and other intellectual property rights (IPRs) act as barriers to new manufacturers and especially developing country vaccine manufacturers (DCVMs), particularly for the HPV, rotavirus, and pneumococcal conjugate vaccines. The objectives of the study were to (1) identify documented and potential effects, if any, of IPRs (in particular patents) on access to essential vaccine technologies that enable manufacturers to develop new vaccines; (2) identify perceived barriers that may deter or delay market entry of manufacturers.

2. Methods

The study used three approaches: (1) literature surveys to identify potential barriers that IPRs may create for research, development, and commercialization of novel vaccines and/or combinations of existing vaccines by competitive suppliers. This included a review of peer-reviewed papers, and policy documents relevant to vaccine development and intellectual property. Researchers evaluated existing mechanisms to promote vaccine development and purchasing of vaccines for Gavi eligible countries through the reduction of IPRs barriers, including the TRIPS flexibilities (See Supplementary Data for details of literature review).

(2) Case studies to assess and analyze the impact of IPRs on the development of HPV, rotavirus, and pneumococcal conjugate vaccines. These vaccines were chosen because they are relatively new and have been prioritized for Gavi funding. They also have been cited as having complex IP landscapes [6]. The research included unstructured interviews with expert informants, such as researchers, technology transfer professionals, representatives of public health agencies, and developing country vaccine manufacturers (See Supplementary Data for details of methods used for interview study and qualitative analysis). To build a patent landscape, a search was made for US patents or international patent applications (PCT) using keywords in the description and claims of patent documents. Given the various technologies that go into manufacturing a vaccine, the keywords used were deliberately broad in order to capture as many relevant patents as possible. Inventor and names were also used to build upon key word searches. Additional searches used names of companies currently marketing these vaccines as "assignee/applicant". Patent searches were focused on three countries, India, Brazil and China, with established vaccine manufacturing capacity from which Gavi already procures or plans to procure vaccines and in which manufacturers are known to work on the development of one or more of the three vaccines reviewed in the case studies. Patent data are current as of June 30 2012 (See Supplementary Data for details of methods used for building patent landscapes). WIPO recently released a report with patent landscapes of vaccines, which included the pneumococcal vaccines but not HPV and rotavirus vaccines [7]. The WIPO analysis was conducted at the same time as our study and while we identified a similar number of Patent Cooperation Treaty (PCT) applications as the WIPO report, some differences were observed between the PCV landscapes as a result of different searching strategies.

(3) An analysis of the landscape of stakeholders and policy proposals for reducing IPR barriers to facilitate development of new and underutilized vaccines. This included literature reviews and interviews with expert informants representing important stakeholder groups to solicit views on needs related to IPR management and potential solutions.

3. Results

3.1. Human papillomavirus vaccine

We identified 93 patents filed in the US or as PCT applications that would be relevant to the manufacturing of HPV vaccines. Of these the largest number of applications (43) has been filed in China. China also has the highest number of granted patents (16). Brazil has only granted one patent to date out of 31 filed. India has granted 13 out of the 30 applications filed (Fig. 1). Not surprisingly, the two companies with licensed HPV vaccines, GlaxoSmithKline (GSK) and Merck, dominate the patenting activity for HPV vaccine technologies in Brazil, China, and India (Supplementary Table 1–3).

Although the patent landscape for HPV vaccines is quite complex, the analysis suggests patents should not completely block new manufacturers from producing biosimilar vaccines based on major virus capsid protein L1 virus like particles (VLPs) equivalent to Cervarix and Gardasil or second-generation vaccines based on L2 capsid protein VLPs. However, given the number of patents identified and the subjective nature of claims interpretation, new manufacturers and in particular DCVMs do face uncertainty in navigating these patents, which could increase transaction costs and/or delay end products coming to market. Working around some key patents may also add costs and time to the development process.

For example, representatives of one Indian manufacturer stated that while their in-house preliminary FTO analysis suggested there was freedom to operate for developing an LI VLP-based bivalent or quadrivalent vaccine in India, patents filed by GSK separately claim a "Two dose regimen" for compositions containing HPV 16 and 18 VLPs and "providing cross-protection against other oncogenic HPV strains" such as HPV 31, 33, 45, 52, and 58 [8]. The manufacturer indicated that the scope of these patent claims is unclear and the patent status, particularly in other developing countries, are not fully known. Protection against HPV 33, 45, 52, and 58 is especially relevant to vaccines made for developing countries as epidemiological studies show these strains are highly prevalent in parts of Asia and Africa [9].

3.2. Rotavirus vaccine

We identified 29 patents filed in the US or as PCT applications that may be relevant to the manufacturing of rotavirus vaccines. GSK, the manufacturer of the vaccine Rotarix, has the most number of patents filed across the three countries. Merck, the manufacturer of Rotateq, does not appear to have any patents granted in Brazil, China, or India (Supplementary Table 1–3). Our landscape includes patents on technology underlying the bovine reassortant rotavirus vaccine (BRV) owned by the United States National Institutes of Health (NIH). This patent has been refused in Brazil, but is under appeal, and has been granted in China and India where it has been licensed to a number of developing country vaccine manufactures (DCVMs). SII and Bharat Biotech have filed applications for their vaccine candidates as well.

Based on analysis of the patent landscape, there do not appear to be any patent related barriers in Brazil, China, or India that would prevent the production of a BRV. However, new manufacturers seeking to make follow on versions of GSK's Rotarix vaccine may have to work around some of these patents depending on which markets they plan to sell their vaccines in. Representatives of WHO [10] also highlighted that patents on a liquid formulation for a rotavirus vaccine could be an impediment. Merck has broad patent claims on a liquid formulation of BRV, which have been

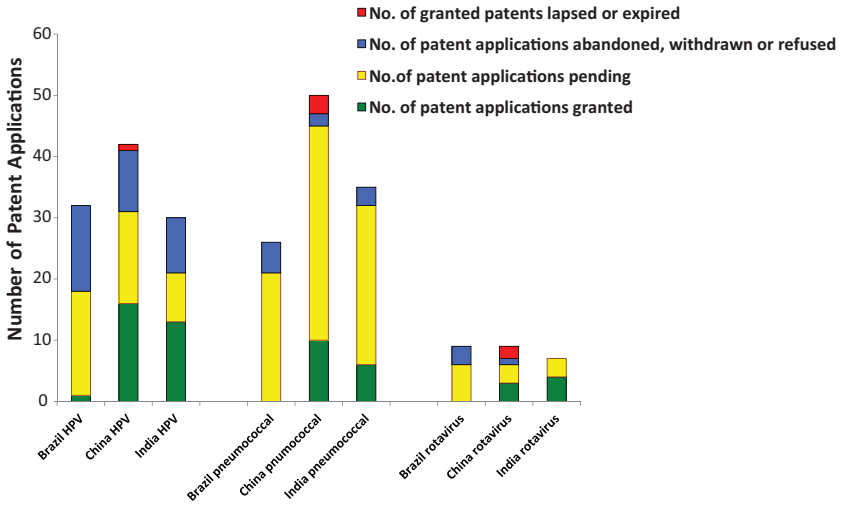

Fig. 1. Status of Patent Applications for HPV, Pneumococcal Conjugate and Rotavirus Vaccines in Brazil, China and India.

filed in many developing countries [11]. Although this study did not find any patent on a liquid formulation awarded to Merck in Brazil, China, or India, it remains possible that Merck has received protection for this technology in other developing countries and the patent may be important depending on the markets in which manufacturers plan to sell their vaccines.

3.3. *Pneumococcal conjugate vaccine*

This vaccine has by far the most patenting activity of the three vaccines. Our study identified 106 PCT applications potentially relevant to the manufacturing of pneumococcal vaccines. GSK, the manufacturer of Synflorix, has filed the most number of patents. GSK has received several patents in China and India, but none as yet in Brazil. Pfizer (previously Wyeth), the manufacturer of Prevnar, has the second most number of patents filed across the three countries (Supplementary Table 1–3).

The patent landscape around pneumococcal vaccines in Brazil, China, and India is complex with GSK in particular owning a large number of patents. Panacea Biotech has challenged one of GSK's patent applications in India [12]. Based on the analysis of the patent landscape and from experiences of stakeholders, it is clear that DCVMs face significant patent related impediments for producing alternative pneumococcal conjugate vaccines. While some manufacturers like Panacea have taken a more aggressive approach by challenging key patents, others appear mainly to be working around them. A number of DCVMs are engaged in product development partnerships for pneumococcal vaccines. The pneumococcal vaccine project at PATH supported by the Bill & Melinda Gates Foundation supports SII and the collaboration between the Chengdu Institute (China) and the Biovac Institute (South Africa) [13,14]. SII is developing two different pneumococcal conjugate vaccine and according to a representative of PATH, SII conducted a detailed FTO analysis and also worked around several patents. One of the important steps in enabling SII's vaccine development was licensing technology for expression of recombinant protein that will be used as a carrier protein for their polysaccharide conjugate vaccine from Pfenex [15]. SII identified this technology early in the development process because they were trying to reduce their risk of infringing patents.

PATH is working with Butantan on developing a whole cell inactivated pneumococcal vaccine and confirmed that there are no IP barriers for developing this vaccine. As representatives of PATH indicated, owning or co-owning the patent is one IP management strategy that PATH uses for increasing access to vaccine technologies for DCVMs [16].

Additionally, Butantan is developing a pneumococcal conjugate vaccine focusing on serotypes most prevalent in Brazil. Patent issues were encountered and Butantan had to develop their own conjugation methods. IP issues were also encountered for one of the proteins, pneumolysin, which Butantan had planned to use in this vaccine. The process of working around these patents added time to their process but did not appear to significantly delay the product development [17].

A vaccine manufacturer from India stated that in their combined FTO analysis, several patents filed by GSK and Pfizer in India and other developing countries were flagged as potential impediments. The manufacturer, however, found ways to work around these patents and developed several new technologies during their R&D process, in part to avoid infringing patents. Representatives indicated that patents on conjugation methods were perhaps the most challenging to work around in terms of both time and effort required [8].

4. Discussion

Findings from this study demonstrate that DCVMs remain concerned about uncertainties surrounding patent claims and face difficulties in assessing the complex IP space of the human papillomavirus (HPV), rotavirus, and pneumococcal conjugate vaccines. The concerns are most pronounced for pneumococcal conjugate vaccines, the area with the most patenting activity. As such, patents can present obstacles to new manufacturers from developing countries that wish to enter the market in any step of the development process starting from preclinical R&D, to scale up, formulation and licensure in the markets of choice, and hence may alter their decision pathways of independent development or seeking access to IPRs through licensing at each step [18].

However, the extent to which patent barriers are rated limiting or surmountable, likely varies for each vaccine. Some manufacturers expressed that patents created uncertainty and navigating them increased transaction costs and added to their development timelines. Other experts believe that the challenges patents present could be worked around or removed through the right legal frameworks due to their lack of inventiveness.

These differing views beg the question, what constitutes a barrier? Is it only when a patent cannot be worked around? Or are patents a barrier when they add uncertainty or delay competition?

These questions need to be explored further as the current narratives do not address this nuance. Our findings suggest that in the case of some vaccines (HPV and pneumococcal) patents create impediments. More worryingly, following the continued liberalization of IPRs and trade laws, patents could increasingly become a barrier for new vaccine development. This is reflected in the pneumococcal and HPV patent landscapes and the increasing number of patents being filed by multinational companies.

The authors of the study therefore identified the following steps to better understand and reduce IP barriers (real or perceived) in order to improve competition in the vaccines marketplace. It must be underlined that these recommendations represent the views of the authors and does not commit Gavi or any of its partners.

4.1. (i) Encourage efforts to improve patent transparency

The study found a need for improved transparency around patenting of vaccine related technologies. At present there is no mechanism or provision available online to access information pertaining to "Complete list of countries a particular patent application has been filed". Obtaining such information remains a concern in making decisions about freedom to operate in potential markets. One potential solution is to establish a partnership with WIPO under its "Development Agenda Project on Developing Tools for Access to Patent Information" and support the development of a public database for the three vaccines studied here [19]. While such information may not amount to the standard required to make freedom to operate (FTO) decisions it could help reduce the time and resources spent on such issues (the patent landscapes created through the study will be made publicly available by the authors).

4.2. (ii) Encourage IPR management capacity building efforts for DCVMs

This study identified that DCVMs have highly variable resources and capacities for IP management. Particular areas of need raised by DCVMs include information about licensing negotiations to improve technology transfer. Supporting and augmenting these capacities through training and development of resources like a casebook on best practices for IPRs management specifically for vaccine technologies is recommended. Technical support could also include engaging legal experts in governments, nonprofit, and industrial sectors (e.g., pharmaceutical companies) outside of governments who may be willing to provide services (pro bono, at low cost or paid for by third parties) for important activities like legal interpretation and risk assessment. Engaging with vaccine research and development funders, universities and nonprofit institutions on IPR management issues may further help the development of resources and identify opportunities for policy development.

4.3. (iii) Encourage technical support to developing countries in the use of TRIPS flexibilities and in the design of IP laws

Since the current environment of free trade agreements may further heighten IP barriers, patents may play a bigger role in the future in influencing manufacturers' decisions to develop innovative vaccines in a timely manner. As more patents are filed they may become an obstacle (whether granted or not) simply by creating a level of uncertainty that is not a feasible risk to some manufacturers. Increased filing of patent applications with broad claims or which are not merited because they are not new or lack inventiveness could also deter companies or governments from supporting innovative vaccine development. The latter may have other negative consequences, such as creating mistrust among governments in developing countries on collaborative vaccine development projects [20]. It is important for the vaccine community to provide technical support to developing country governments in the creation of IP laws that not only support innovation and respect international law but also safeguard public health access against unmerited patents. Indeed, as has been demonstrated in other disease areas where patents have posed problems to access, creating patent laws with stricter patentability criteria that weed out low quality patents can help remove some of the barriers. Although we do not go into discussion about the merits of the patents covered in this study, our preliminary review of some of the patents and their prosecution histories show them to be lacking merit with claims not meeting patentability criteria. Stricter legal standards for patentability that TRIPS flexibilities permit can remedy such patents becoming barriers.

4.4. (iv) Continue to monitor and further explore how IPR issues are affecting vaccine development

There is a dearth of empirical data on whether and exactly how IP and in particular patents, affect vaccine R&D projects. While studies like this one provide a "snapshot," continuous engagement with appropriate stakeholders will generate greater insight. Further empirical studies may be needed on IP issues with respect to emerging vaccines to anticipate any potential barriers. Furthermore, given trends of increased patenting of vaccine technologies and the evolving landscape of vaccine manufacturing itself, such stakeholder engagement and IP monitoring will allow for policy-making that is grounded in real-world experiences.

There are some limitations that must be considered while interpreting the findings from this study. First, the study focused on DCVMs in India, China, and Brazil and cannot be generalized to all DCVMs or vaccine manufacturers. Second, some manufacturers did not respond to interview requests and we cannot generalize our findings to all DCVMs even within a country. Furthermore, those interviewed may not have fully disclosed details of their IPRs management strategies in order to protect their competitive advantage or confidentiality agreements. Third, the study did not extensively sample public funders of vaccine research or NGOs involved in vaccine development. Finally, as with all methodologies for patent searching there are a number of limitations for this landscape. Given the various technologies that contribute to each vaccine, even broad search terms may not capture patents for some technologies, patent databases may not always be up to date and information obtained may have errors. In view of these limitations, the patent landscapes in the study should not be taken as legal advice or as a freedom to operate (FTO) opinion. Nevertheless, they may constitute a useful starting point to conduct more in-depth analysis and the patent landscapes may serve as a base for more detailed analysis of patenting behavior.

5. Conclusion

This study found that IPRs, particularly patents or perceptions thereof, can create obstacles for developing country vaccine manufacturers to enter into the vaccine market. Based on our findings, we suggest that improved transparency around patenting of vaccine technologies, stricter patentability criteria suited to local needs and strengthening of IPRs management capabilities where relevant, may be necessary in order to reduce patent related impediments. Greater attention to these issues through technical support in IP management and FTO analyses, monitoring developments in the industry and sustained engagement with stakeholders for systematic need assessment and identifying solutions can help encourage a competitive supplier base for quality vaccines at sustainably low prices.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2015.08.063.

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